University of Southampton

Clinical Pharmacology Group

Dr Andrew Renwick
Reader in Clinical Pharmacology
Head of Group

University of Southampton
Biomedical Sciences Building
Bassett Crescent East
Southampton
SO16 7PX
United Kingdom

Telephone +44 (0)1703 594272
Fax +44 (0)1703 594262
Email agr@soton.ac.uk

Dr CW Jameson
National Toxicology Program
Report on Carcinogens
MD WC-05
PO Box 12233
Research Triangle Park
NC 27709
USA

31 July 1997

Dear Dr Jameson

NTP's Biennial Report on Carcinogens (BRC), Ninth Edition

I understand that the NTP has announced its intention to delist saccharin from the Report on Carcinogens and I wish to support most strongly the deleting of saccharin.

I have been actively involved in research on saccharin for over 20 years, in relation to the increase in bladder tumours found in rats given high dietary concentrations of sodium saccharin. My own research has been in the area of metabolism and kinetics, and I have noted with great interest the numerous mechanistic studies which have contributed to our understanding of the basic biology of the phenomenon and most importantly its relevance to humans. I am convinced that the toxicology of sodium saccharin has contributed to the maturation of risk assessment procedures and led to more rational application of scientific data.

I would draw to your attention the WHO/FAO Joint Expert Committee on Food Additives (JECFA) evaluation of saccharin in 1993 (WHO Food Additives Series, 32, pp105-133) which concluded that "*it would be inappropriate to consider the bladder tumours induced in male rats by sodium saccharin to be relevant to the assessment of toxicological hazard to humans*". Research published since the evaluation has supported this conclusion.

The excellent work of Professor Sam Cohen and other workers has demonstrated clearly that the bladder responses in rats arise from alteration of the urinary physiology and are not a direct effect of the saccharin anion. The facts that the bladder effects are dependent totally on the salt form given, and that acid saccharin is inactive, are incompatible with saccharin being the active entity. Saccharin is a strong organic acid (although the free acid is sparingly water soluble), and the ionic form of saccharin present in physiological media is not dependent on the salt form administered. As such, the saccharin anion (to which tissues would be exposed) **cannot** be regarded as a carcinogen, even in rats, because the acid form (which shows similar kinetics to the sodium salt) is devoid of activity.

The delisting of saccharin is both logical and scientific; both in relation to human risk assessment and also in relation to animal carcinogens - the saccharin anion is simply the vehicle for producing an increase in urine pH and other changes in the rat urinary bladder.. If saccharin is not delisted then I would suggest that other active sodium salts such as vitamin C are also listed as carcinogens - and how do we give sensible public health advice if that is true?

Finally, you should be aware that because of my research with sweeteners, I have acted and continue to act as a scientific consultant to the International Sweeteners Association in Brussels. However, I am writing this letter as one of the international scientists actively involved in saccharin research and it is an expression of my personal opinion on the basis of the scientific data, and represents my independent view.

Yours sincerely

AG Renwick
Professor of Biochemical Pharmacology